INTERVIEW

Ruben A Mesa, MD

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Tracks 1-13

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DR LOVE: Would you provide a brief overview of myeloproliferative neoplasms (MPNs) in general and more specifically of the evolution of JAK2 inhibitors in myelofibrosis (MF)?

DR MESA: I view MPNs as a group of chronic leukemias that can progress to acute leukemia. In MPNs, particularly in MF, the bone marrow becomes "leaky." Cells that ordinarily reside in the bone marrow leak out into the blood circulation and become trapped in the spleen. A misperception in the past has been that the spleen is enlarged as a result of anemia.

To provide some perspective, for a long time the only options for MF were either off-label medicines indicated for other cancers or clinical trials with agents being developed for other indications, such as myelodysplastic syndromes (MDS) or acute myeloid leukemia. Historically, we've had to "beg, borrow and steal" to have medicines to evaluate in MPNs. In large part, those trials were unsuccessful.

The watershed moment for these diseases came in 2005 when we started to make some inroads into understanding the pathogenesis of the disorders with the discovery of the JAK2 V617F mutation, which provided a "druggable target." JAK2 is part of the JAK-STAT pathway, which can be thought of as a tyrosine kinase pathway that acts as a stimulus for cells to grow and divide, parallel to our understanding of BCR-ABL in patients with chronic myeloid leukemia.

At this point, we believe the JAK2 mutation to be a "middle step" in the story. It's probably not the change that initiates the disease. Our understanding of the pathogenesis remains incomplete.

ASCO 2011 was particularly exciting in that it was the first time randomized Phase III trials have ever been performed in MF on any level, let alone with the success that was reported. Two important studies were presented, the first of which — and one for which I was a co-principal investigator — was ruxolitinib versus placebo for patients with intermediate- and high-risk MF.

This study demonstrated that ruxolitinib was quite potent in decreasing the massive splenomegaly associated with MF — a 42% improvement in this primary endpoint was observed versus placebo. Ruxolitinib was also potent in improving the significant symptoms that patients may experience with

1.1

Phase III Trial Results with the JAK1/2 Inhibitor Ruxolitinib for Patients with Myelofibrosis (MF), Postpolycythemia Vera MF or Postessential Thrombocythemia MF

	COMFORT-I[1]		COMFORT-II[2]	
Efficacy — Primary endpoint	Ruxolitinib (n = 155)	Placebo (n = 153)	Ruxolitinib (n = 146)	BAT (n = 73)
Patients with ≥35% decrease in spleen volume at 24 weeks[1] and 48 weeks[2]	41.9%	0.7%	28.5%	0%
	$p < 0.0001$		$p < 0.001$	
Quality of life — Exploratory endpoint				
Patients with ≥50% decrease in symptom score	45.9%	5.3%	—	
	$p < 0.0001$			

BAT = best available therapy

Symptom score = sum of scores for itching, night sweats, bone/muscle pain, abdominal discomfort, pain under the left ribs and early satiety

[1] Verstovsek S et al. *Proc ASCO* 2011;**Abstract 6500**; [2] Harrison CN et al. *Proc ASCO* 2011;**Abstract LBA6501**.

the illness, such as fatigue, night sweats and weight loss (Verstovsek 2011; [1.1]). Patients also experienced improvement in cachexia and recovery from abnormal decreases in their cholesterol.

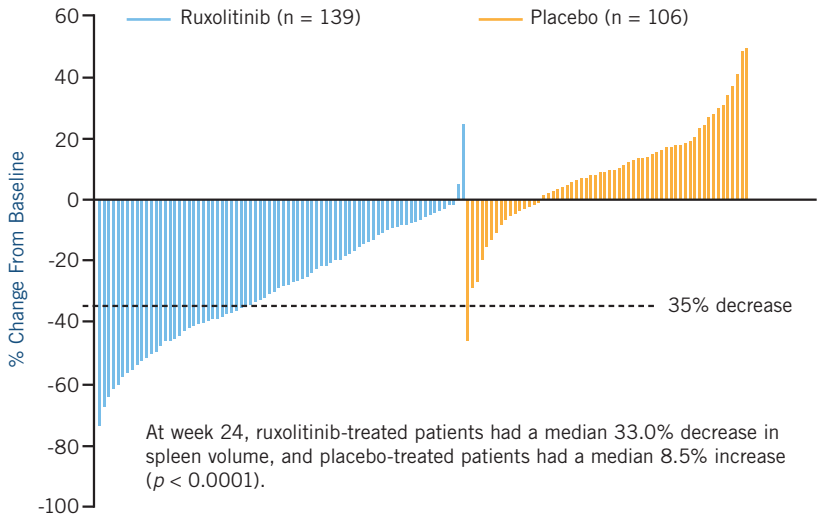
As we evaluate new agents, we ask ourselves: Does everyone benefit, or does a clear group benefit and another doesn't? I'd say with ruxolitinib and the other JAK2 inhibitors, we tend to see that the vast majority of patients experience a benefit. As we evaluate the waterfall plot, we see that the majority of patients have a decrease in spleen volume (Verstovsek 2011; [1.2]).

The other study presented was the European version of the trial — ruxolitinib versus physician's choice of alternative therapy in primary MF, postpolycythemia vera MF or postessential thrombocytopenia MF. Even against an active control arm of best available therapy, the results basically were interchangeable — dramatic improvements in the size of the spleen and a dramatic difference in terms of improvement in symptoms (Harrison 2011; [1.1]).

In terms of toxicities, both ruxolitinib and JAK2 inhibitors as a class across the spectrum of MPNs have variable degrees of myelosuppression. All the JAK2 inhibitors have a real dose-dependency issue, and we need to balance the need to administer enough JAK2 inhibitor to attain a benefit with that of avoiding dropping the red cell count or causing anemia or thrombocytopenia. For most of them, including ruxolitinib, the dose-limiting toxicity is thrombocytopenia. With the randomized study, we had already ascertained the optimal dosing, and 2 different dose levels were used depending on patients' platelet

1.2

COMFORT-I: Percent Change in Spleen Volume from Baseline in Response to Ruxolitinib versus Placebo in Patients with Myelofibrosis



With permission from Verstovsek S et al. *Proc ASCO* 2011;**Abstract 6500**.

counts. We found that anemia and thrombocytopenia were uncommon, with a prevalence of clearly less than 20% and in some cases less than 10% (Verstovsek 2011).

Track 9

DR LOVE: What role do immunomodulatory drugs (IMiDs) play in the treatment of MF?

DR MESA: All of the IMiDs — thalidomide, lenalidomide and now pomalidomide — have been active both in myeloma and MF. IMiDs have a variety of effects, but they certainly affect cytokines. Their benefit in MF has largely been improvement in cytopenias — anemia and thrombocytopenia. The current speculation is that inhibition of cytokines changes the bone marrow milieu and allows for more effective hematopoiesis to occur.

We've performed successful studies with lenalidomide in MF, and it is interesting that, like patients with MDS and deletion 5q, individuals with MF and deletion 5q can experience significant benefits with lenalidomide therapy (Tefferi 2007). Lenalidomide can also be helpful in other patients with MF, but the myelosuppressive effects of lenalidomide can sometimes be limiting.

Thus, we evaluated pomalidomide and found that low doses of pomalidomide are well tolerated and improve anemia and transfusion dependence in patients with MF (Tefferi 2009). The international Phase III RESUME trial is now evaluating pomalidomide versus placebo in more than 200 patients with MF and anemia.

DR LOVE: In which clinical situations have you used these agents for MF outside a protocol setting?

DR MESA: Thalidomide/prednisone is particularly effective in individuals with severe thrombocytopenia. I recently administered this combination to a patient with platelet transfusion dependence and anemia. I consider lenalidomide off study, particularly if a deletion 5q is in the karyotype or if the patient has refractory anemia. And unlike thalidomide, lenalidomide can potentially benefit patients with splenomegaly. ■

SELECT PUBLICATIONS

Harrison CN et al. **Results of a randomized study of the JAK inhibitor ruxolitinib (INC424) versus best available therapy (BAT) in primary myelofibrosis (PMF), post-polycythemia vera-myelofibrosis (PPV-MF) or post-essential thrombocythemia-myelofibrosis (PET-MF).** *Proc ASCO* 2011;**Abstract LBA6501**.

Tefferi A et al. **Pomalidomide is active in the treatment of anemia associated with myelofibrosis.** *J Clin Oncol* 2009;27(27):4563-9.

Tefferi A et al. **Lenalidomide therapy in del(5)(q31)-associated myelofibrosis: Cytogenetic and JAK2V617F molecular remissions.** *Leukemia* 2007;21(8):1827-8.

Verstovsek S et al. **Results of COMFORT-I, a randomized double-blind phase III trial of JAK 1/2 inhibitor INCB18424 (424) versus placebo (PB) for patients with myelofibrosis (MF).** *Proc ASCO* 2011;**Abstract 6500**.